REMARKS

This Amendment is in response to the Office Action, dated May 21, 2009 ("Office Action"). Claims 1, 13, 18, 34, 35 and 39 are amended, claims 12, 17, 33 and 37 are canceled and claims 40-43 are added by virtue of the present amendment. No new matter is added. Examination and allowance of the claims in view of the ensuing remarks are respectfully requested.

Claims 1, 13, 18, and 34 have been amended to direct the claims to neural stem cells (NSCs). No new matter is added. Support for this amendment can be found throughout the specification; for example, page 2, lines 9-29, page 5, lines 10-33, and page 11, lines 11-20.

Claim 35 has been amended to correct a grammatical error.

Claim 39 has been amended to be consistent with the amendment to claim 1.

Claims 40-42 have been added to further recite that the NSC does not express EAAT1/EAAT2. No new matter is added. Support for this amendment can be found through the specification; for example, page 23, lines 14-17.

Claim 43 has been added to further recite that the NSCs exhibit an A2B5 astrocytic precursor marker and do not express EAAT1/EAAT2. No new matter is added. Support for this amendment can be found through the specification; for example, page 23, lines 14-17.

In the Office Action, the Examiner acknowledged Applicants' election of Group I, readable upon claims 1-12 and 34-39, and drawn to isolated stem cells and kits comprising isolated stem cells. The Examiner also acknowledged Applicants' election of species readable upon claims 1-3, 5-9, 12, and 34-39, drawn to A2B5 as the astrocytic precursor marker, IL-12 as the heterologous gene encoding a polypeptide for therapeutic use, and glioblastoma multiforme as the disease condition.

As provided in MPEP § 821.04(b), withdrawn process claims that depend from or otherwise require all the limitations of an allowable product claim can be considered for rejoinder. This would include Group II, readable upon claims 13-17 and new claim 41, drawn to methods of assessing tumor tropic potential and Group III, readable upon claims 18-32 and new claim 42, drawn to methods treating a disease condition.

Accordingly, Applicants request that withdrawn process claims 13-32 and new claims 41-42 be rejoined when the product claims are found allowable.

The Examiner rejects claims 1-3, 5, 6, 12, and 34-39 under §102(b), as allegedly being anticipated by Lapidot *et al.* (U.S. Patent No. 7,101,708), as evidenced by Kemshead *et al.* (INT. J. CANCER. (1981), 27:447-52). The Examiner contends that the pending claims are product-by-process claims and that prior art disclosing the product will destroy novelty, even if the prior art recites a process different than the process steps recited in the pending claims. The Examiner contends that Lapidot *et al.* discloses isolated CXCR4-expressing ("CXCR4+") progenitors and stem cells that are responsive to SDF-1. The Examiner further contends that Lapidot *et al.* discloses the use of stem cells expressing a heterologous gene for the treatment of malignancies. In addition, the Examiner relies upon Kemshead *et al.* to contend that markers (e.g., A2B5) and neural stem cell subtypes are inherent features of stem cells. With respect to claims 1-3, 5, 6, 34-36, 38 and 39, Applicants respectfully traverse this rejection. With respect to canceled claims 12 and 37, the rejection is rendered moot.

A claim is anticipated if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). With respect to inherency, the Examiner must provide rationale or evidence tending to show inherency. MPEP §2112(IV). "In relying upon the theory of inherency, the examiner must provide a basis in the fact and/or technical reasoning to reasonably support the determination that the alleged inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP §2112(IV) (citing *Ex parte* Levy, 17 USPQ2d 1461, 1464 (BPAI 1990). "The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." MPEP §2112(IV) (emphasis in original) (citing *In re* Rijckaert, 9 F.3d 1531, 1534 (Fed. Cir. 1993)). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The

mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" MPEP §2112(IV) (emphasis added) (citing *In re* Robertson, 169 F.3d 743, 745, 49 USPQ 2d 1949, 1950-51 (Fed. Cir. 1999)). Furthermore, inherent anticipation is only proper in limited instances where a prior reference naturally results in the claimed invention as a matter of fact. *Schering v. Geneva*, 339 F.3d 1373 (Fed. Cir. 2003).

Applicants submit that in view of the present amendment, claims 1-3, 5, 6, 34-36, 38 and 39 are not anticipated by Lapidot *et al.*, as evidenced by Kemshead *et al.* While Applicants do not concede to the merits of the Examiner's rejection, in an effort to advance prosecution, claims 1-3, 5, 6, 34-36, 38 and 39 have been amended to direct the claims to neural stem cells. Thus, these particular cells distinguish the invention from the cited references. Applicants respectfully submit that Lapidot *et al.*, as evidenced by Kemshead *et al.* is distinguishable on the basis that none of the cited references expressly disclose a CXCR4+ neural stem cell. Rather, Lapidot *et al.* focuses squarely on isolation of CXCR4+ hematopoietic stem cells.

With regards to the allegation that CXCR4+ hematopoietic stem cells in Lapidot *et al.* inherently anticipate the rejected claims, as evidenced by the A2B5 stem cell marker disclosed in Kemshead *et al.*, we respectfully submit that the Examiner has mistakenly interpreted the presence of A2B5 reactivity in hematopoietic leukemic marrow cells. Indeed, hematopoietic cells described by Kemshead *et al.* do not express A2B5. Rather, Kemshead *et al.* states that antibody A2B5 shows no reactivity to a panel of human leukemic cell lines or normal human bone marrow. Thus, human leukemic cells and human bone marrow cells described by Kemshead *et al.* do not express A2B5. Kemshead *et al.* teaches the use of antibody A2B5 to remove tumor cells that express A2B5 from hematopoietic cells so that the hematopoietic cells (which will not be removed because they do not express A2B5) will be free of tumor cells. Consequently, Kemshead *et al.* cannot evidence the presence of A2B5 in the hematopoietic stem cells in Lapidot *et al.* Assuming *arguendo* that the Examiner may have cited Kemshead *et al.* to show the presence of A2B5 in cells of neural origin, we remind Examiner that neuroblastoma cells are tumor cancer cells, whereas the claimed invention is directed to neural stem cells. As well-understood in the art and recognized

in Kemshead *et al.*, different types of cells express different markers. The reliance on Kemshead *et al.* fails to provide any evidence to show that A2B5 is expressed by hematopoietic stem cells. Furthermore, Lapidot *et al.* also does not disclose a therapeutic kit that includes a quantity of SDF-1 to anticipate claim 38.

With regards to the allegation that neural stem cell subtypes are inherent features of stem cells, as evidenced by Kemshead *et al.*, Applicants submit that Examiner was similarly mistaken. There is no disclosure by Kemshead *et al.* of a neural stem cell subtype. We remind the Examiner that it is not sufficient for the missing disclosure to possibly result in the claimed invention; rather it must be present through reason or evidence showing inherency. In light of the foregoing, Applicants request withdrawal of the rejections under 35 U.S.C. §102(b).

The Examiner rejects claims 1-3, 5, 6, 12, 34-37, and 39 under §102(e), as allegedly being anticipated by Suda *et al.* (U.S. Pat. App. Pub. No. 2007/0053884 A1). It appears that Examiner is also relying upon Kemshead *et al.* to allege that markers (e.g., A2B5) and neural stem cell subtypes are inherent features of stem cells. The Examiner contends that Suda *et al.* discloses isolated CXCR4+ progenitors and stem cells that are responsive to SDF-1. The Examiner further contends that Suda *et al.* discloses the capacity of the CXCR4+ stem cells to differentiate into neural stem cells, as well as the application of isolated CXCR4+ stem cells for disease treatments. The Examiner again contends that markers (e.g., A2B5) and neural stem cell subtypes are inherent features of stem cells, as evidenced by Kemshead *et al.* With respect to claims 1-3, 5, 6, 34-36 and 39, Applicants respectfully traverse these rejections. With respect to canceled claims 12 and 37, the rejection is rendered moot.

Applicants submit that in view of the present amendment, claims 1-3, 5, 6, 34-36 and 39 are not anticipated by Suda *et al.*, as evidenced by Kemshead *et al.* While Applicants do not concede to the merits of the Examiner's rejection, in an effort to advance prosecution, claims 1-3, 5, 6, 34-36 and 39 have been amended to direct the claims towards neural stem cells. Thus, these particular cells are distinguishable from the cited references. Applicants respectfully submit that Suda *et al.* is distinguishable on the basis that it does not disclose CXCR4+ neural stem cells. Rather, Suda *et al.*

discloses isolation of CXCR4+ multi-potent cells. Applicants respectfully submit that Suda *et al.* as evidenced by Kemshead *et al.* cannot inherently anticipate these claims. As discussed *supra*, Kemshead *et al.* states that antibody A2B5 shows no reactivity to a panel of human leukemic cell lines or normal human bone marrow. Kemshead *et al.* does not provide any evidence that A2B5 expression and/or neural stem cell subtypes are inherent features of the multi-potent cells disclosed by Suda *et al.* Thus, Kemshead *et al.* cannot evidence the presence of A2B5 in progenitors and stem cells in Suda *et al.* In light of the foregoing, Applicants request withdrawal of the rejections under 35 U.S.C. §102(e).

The Examiner rejects claims 2 and 5-8 for an alleged failure to satisfy the written description requirement under §112, first paragraph. The Examiner contends that claims directed to cells with various markers or expressing heterologous genes are not sufficiently described in the specification to reasonably convey possession of the invention. More specifically, the Examiner contends that limitations reciting "markers" (i.e., claim 2) or a "heterologous gene" (i.e., claim 5) do not provide any further conserved structure and thus, do not provide sufficient distinguishing identifying features of the claimed genus of molecules. Furthermore, the Examiner contends that the specification does not adequately support claims 6-8, which are directed to therapeutic proteins that are cytotoxic and/or involved in immune responses. Applicants respectfully traverse this rejection.

Applicants submit that claims 2 and 5-8 satisfy the written description requirement under §112, first paragraph. One of skill in the art readily understands that "markers," as used in claim 2, are proteins that identify a neural stem cell that is an astrocytic precursor cell. One of skill in the art will appreciate the different markers that are used to differentiate different types of cells. [*See e.g.*, definition of "markers" from NIH Regenerative Medicine Report, Appendix E; appended hereto as Exhibit A.] Applicants note that in applying the written description requirement as taught by the Written Description Training Materials, Revision 1 (March 25, 2008) published by the USPTO, on pages 1-2, it notes "For each claim drawn to a genus, consider each of the above factors to determine whether there is disclosure of a representative number of

species which would lead one skilled in the art to conclude that the applicant was in possession of the claimed invention. The number of species required to represent a genus will vary, depending on the level of skill and knowledge in the art and the variability among the claimed genus. For instance, fewer species will be required where the skill and knowledge in the art is high, and more species will be required where the claimed genus is highly variable." (Emphasis added). Claim 2 is directed to neural stem cells that are astrocytic precursors and Applicants have enumerated a number of markers to characterize them. [*See e.g.*, page 11, lines 15-28, and pages 21-23.] Applicants submit that the knowledge in the art of determining what constitutes a "marker" that identifies a neural stem cell as an astrocytic precursor is high. One of skill in the art would readily recognize proteins that are markers that identify neural stem cells as astrocytic precursors. This is also not an instance wherein one of skill in the art would be confused and unaware of what constitutes a marker. Furthermore, the specification provides several working examples of "markers" to convey to one skilled in the art that the inventors were in possession of the claimed genus; for example, Example 5, pages 21-23, as further exemplified by Table 1.

Furthermore, one of skill in the art readily understands that "heterologous gene" describes cellular expression of a gene not normally found in that cell type. The present claims are directed to neural stem cells and Applicants have enumerated a number of working examples of "heterologous gene" [*see e.g.*, page 2, lines 30-33, page 8, lines 10-30, and page 13, lines 6-26]. Applicants submit that the knowledge in the art of determining whether a gene is a heterologous gene is extremely high, methods of manipulating cells to express a heterologous gene is extremely high. This is not an instance where one of skilled in the art could not understand what genes are heterologous genes. Furthermore, the specification provides guidance towards use of "heterologous gene," including IL-12, as related to tumor suppression. [*See e.g.*, page 2, lines 30-33, page 3, lines 3-26, and page 13, lines 19-21.] Thus, the exemplary heterologous genes disclosed in the specification to represent the genus of "heterologous gene" is a representative number of species which would lead one skilled in the art to conclude that Applicants were in possession of the claimed invention, including IL-12; for example, Example 5, page 21.

Thus, Applicants respectfully submit that claims 2 and 5-8 comply with 35 U.S.C. §112, first paragraph. In light of the above remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under §112, first paragraph.

The Examiner rejects claim 9 as being allegedly obvious under §103(a) based on Lapidot *et al.* in view of Tahara *et al.* (CANCER RESEARCH (1994), 54:182-189). The Examiner contends that Lapidot *et al.* broadly teaches an isolated composition consisting of CXCR4+ stem cells responsive to SDF-1, but is silent with respect to IL-12 heterologous gene expression. The Examiner further contends that combining Lapidot *et al.* with Tahara *et al.*, which teaches modification of stem cells to express IL-12 for application in tumor growth suppression, makes the present invention obvious. Applicants respectfully traverse this rejection.

A claimed invention is not obvious if the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. *In re Kubin*, Serial No. 09/667,859, 15 (Fed. Cir. 2009) (citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Additionally, the combination of the applied references must teach each and every element of the claim.

Applicants submit that claim 9 is not rendered obvious by Lapidot *et al.* in view of Tahara *et al.* under §103(a). Neither Tahara *et al.* nor Lapidot *et al.* provides sufficient detail to achieve the present invention of CXCR4+ neural stem cells heterologously expressing IL-12. In Lapidot *et al.*, the CXCR4+ stem cells were hematopoietic cells, unlike the neural stem cells of the instant application. Similarly, Tahara *et al.* focuses on using 3T3 fibroblasts expressing IL-12, not neural stem cells. At most, combining the references may provide general guidance towards CXCR4+ hematopoietic stem cells migrating through SDF-1 affinity to deliver heterologous proteins, such as IL-12, to tumor sites. In Lapidot *et al.*, CXCR4+ hematopoietic stem cells did not express a heterologous protein, such as IL-12. Furthermore, there is no disclosure by Tahara *et al.* that the 3T3 fibroblasts expressing IL-12 possessed the ability to migrate or that they migrated through SDF-1 affinity to deliver IL-12 to tumorigenic sites. The combination of references does not teach the CXCR4+ neural stem cells expressing IL-12 as

required by claim 9. In light of the foregoing, Applicants request withdrawal of the rejections under 35 U.S.C. §103(a).

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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Attachment: Department of Health and Human Services (NIH). (REGENERATIVE MEDICINE (2006), Appendix E).